

Natural Herbs and Chemical Drugs in Hypertension Treatment: A Review on the Integration of Traditional Wisdom and Modern Science

Xinyu Feng¹, Yuxin Ji¹, Yan Lin¹, Yu Wang^{1,2}, Xiaomeng Zhang^{1,2}, Bing Zhang^{1,2} and Zhijian Lin^{1,2*}

¹Department of Clinical Chinese Pharmacy, School of Chinese Pharmacy, Beijing University of Chinese Medicine, Beijing 100029, China

²Research Center for Pharmacovigilance and Rational Use of Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China

***Corresponding author:** Zhijian Lin, Department of Clinical Chinese Pharmacy, School of Chinese Pharmacy, Beijing University of Chinese Medicine, Research Center for Pharmacovigilance and Rational Use of Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China

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ABSTRACT

Hypertension is a prevalent global cardiovascular disorder with a complex pathophysiology, necessitating diverse therapeutic approaches. This review systematically examines the integration of traditional herbal medicine and modern chemical drugs in managing hypertension, highlighting the convergence of ancient knowledge and contemporary scientific advancements. Initially, the pathophysiological basis of hypertension is outlined to provide context for therapeutic interventions. The historical use, bioactive constituents, and mechanisms of action of traditional herbs, such as *Butea monosperma*, are explored in detail. These are contrasted with the pharmacodynamics and therapeutic targets of modern antihypertensive agents. Emphasis is placed on bioactive molecules derived from natural sources, including terrestrial plants and marine products, such as polyphenols, flavonoids, alkaloids, and peptides, which modulate vascular tone, oxidative stress, inflammation, and endothelial function at the molecular level. The review further discusses the synergistic potential of combining traditional and chemical therapies and addresses current challenges, such as standardization, safety, and efficacy evaluation. Finally, future directions are proposed, focusing on precision and personalized medicine approaches to optimize hypertension management by leveraging the complementary strengths of traditional herbal remedies and modern pharmacology.

Keywords: Hypertension; Natural Herbs; Chemical Drugs; Bioactive Molecules; Molecular Mechanisms; Traditional Medicine; Targeted Therapy

Abbreviations: CKD: Chronic Kidney Disease; ACEIs: Angiotensin-Converting Enzyme Inhibitors; ARBs: Angiotensin Receptor Blockers; CCBs: Calcium Channel Blockers; TCM: Traditional Chinese Medicine; RAAS: Renin-Angiotensin-Aldosterone System; PRR: Pro Renin Receptor; SNS: Sympathetic Nervous System; PVN: Paraventricular Nucleus; NO: Nitric Oxide; NCC: Na-Cl Cotransporter; TDCS: Transcranial Direct Current Stimulation; UCP1: Uncoupling Protein 1; BMA: *Butea monosperma* Agglutinin; H₂S: Hydrogen Sulfide; ROS: Reactive Oxygen Species; ACE: Angiotensin-Converting Enzyme; PUFAs: Polyunsaturated Fatty Acids; EPA: Particularly Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid; MS: Mass Spectrometry; NMR: Nuclear Magnetic Resonance; SAR: Structure-Activity Relationship; HPLC: High-Performance Liquid Chromatography

Introduction

Hypertension remains a predominant modifiable risk factor for cardiovascular disease worldwide, substantially contributing to morbidity and mortality. Globally, over 1.3 billion individuals are affected by elevated blood pressure, with a significant proportion residing in low- and middle-income countries [1]. The pathophysiology of hypertension is multifactorial, involving genetic predisposition, lifestyle factors such as diet and physical inactivity, and comorbid conditions including obesity, diabetes, and Chronic Kidney Disease (CKD) [2,3]. Despite the availability of a broad spectrum of pharmacological agents, such as Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), Calcium Channel Blockers (CCBs), beta-blockers, and diuretics, optimal blood pressure control remains elusive for many patients due to issues including drug resistance, side effects, and poor adherence [4,5]. Moreover, the complex interplay between hypertension and comorbidities like CKD and metabolic syndrome further complicates management and elevates cardiovascular risk [2,6]. Conventional antihypertensive therapies are effective; however, they are often associated with adverse effects that may impair patient compliance and quality of life. For instance, beta-blockers and CCBs have been linked to an increased risk of depression and sexual dysfunction, which can negatively impact adherence [7,8]. Additionally, the long-term use of certain antihypertensive drugs may influence bone mineral density or carry risks of other systemic effects [9,10]. These challenges underscore the need for complementary or alternative therapeutic strategies that are both efficacious and well tolerated.

Traditional medicine systems, particularly those based on natural products and herbal formulations, have been employed for centuries to manage hypertension and related cardiovascular conditions. In many developing countries, including India, Ghana, Nigeria, and China, a substantial proportion of the population relies on herbal remedies either exclusively or alongside conventional medicines [11-13]. These natural therapies are often perceived as more accessible, cost-effective, and associated with fewer side effects, making them attractive options for chronic disease management [11,14]. For example, Ayurvedic formulations such as Sarp Gandha Mishran and Tengfu Jiangya tablet have demonstrated potential antihypertensive effects in clinical trials [15,16]. Similarly, Traditional Chinese Medicine (TCM) interventions, including herbal decoctions and acupuncture, have shown promise in blood pressure reduction and cardiovascular pro-

tection [17,18]. Modern pharmacological investigations have begun to elucidate the bioactive constituents and mechanisms underlying the antihypertensive effects of various medicinal plants. Phytochemicals such as flavonoids, alkaloids, terpenoids, and polyphenols exert vasorelaxant, antioxidant, anti-inflammatory, and lipid-lowering activities that contribute to cardiovascular health [19-21]. For instance, compounds isolated from *Achillea millefolium*, *Gymnema sylvestre*, and *Vitex negundo* have demonstrated vasodilatory and blood pressure-lowering effects through modulation of nitric oxide pathways, calcium channel blockade, and anti-inflammatory mechanisms [22-24]. Additionally, polysaccharides derived from TCM have been reported to improve hypertension and myocardial function, highlighting the multifaceted nature of herbal interventions [25].

Clinical evidence, although still emerging, supports the adjunctive use of herbal medicines with conventional antihypertensive drugs to enhance their efficacy and reduce adverse effects. Meta-analyses and randomized controlled trials have indicated that integrated approaches combining herbal formulations with standard pharmacotherapy can achieve greater blood pressure reductions and improve patient-reported outcomes [12,16,26]. However, the quality of evidence varies, and methodological limitations in many studies necessitate further rigorous research to establish safety, efficacy, and optimal dosing regimens [27,28]. The integration of traditional herbal medicine with modern pharmacology offers a promising avenue for the management of hypertension. Advances in analytical techniques, such as ultra-performance liquid chromatography and molecular docking, have facilitated the identification and characterization of active phytochemicals, enabling the development of novel therapeutic agents and formulations [29,30]. Furthermore, the application of machine learning and network pharmacology approaches is enhancing the understanding of personalized treatment strategies and herb-drug interactions, which is critical for optimizing patient care [30,31]. In summary, hypertension remains a global health challenge that requires multifaceted management strategies. Traditional herbal medicines, supported by an accumulating body of pharmacological and clinical evidence, represent valuable complementary options that may improve blood pressure control, mitigate cardiovascular risk factors, and enhance patient adherence. Continued interdisciplinary research integrating traditional wisdom with modern scientific methodologies is essential to fully realize the therapeutic potential of herbal medicines in the management of hypertension and cardiovascular diseases (Figure 1).

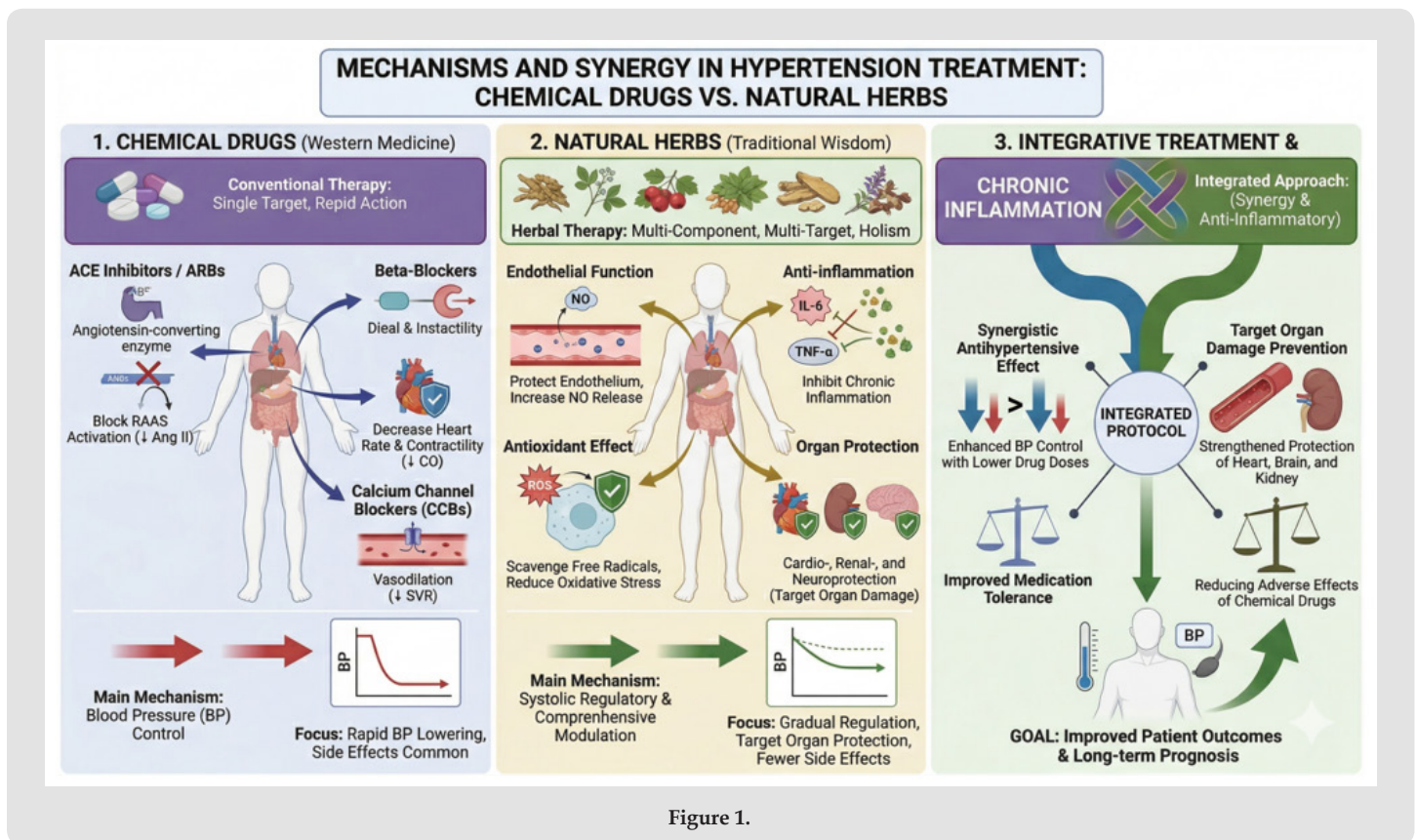


Figure 1.

Overview of the Pathophysiological Basis and Therapeutic Targets of Hypertension

Key Physiological Systems in Blood Pressure Regulation

Blood pressure regulation is a complex physiological process involving multiple interrelated systems that maintain cardiovascular homeostasis. Among these, the Renin-Angiotensin-Aldosterone System (RAAS) plays a central role in long-term blood pressure control. RAAS activation leads to vasoconstriction, sodium and water retention, and vascular remodeling, all of which contribute to elevated blood pressure. The system is initiated by renin release from the kidney, which catalyzes the formation of angiotensin II (Ang II), a potent vasoconstrictor that also stimulates aldosterone secretion from the adrenal cortex. Aldosterone promotes sodium reabsorption in the distal nephron, thereby increasing blood volume and pressure. Dysregulation or overactivation of the RAAS is a hallmark of hypertension and a primary target for chemical antihypertensive agents, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Notably, recent studies have highlighted the role of the (Pro)Renin Receptor (PRR) and its soluble form (sPRR) in modulating intrarenal RAAS activity, influencing sodium handling and blood pressure regulation in a context-dependent manner [32]. Furthermore, the kidney-skin crosstalk has emerged as an important

concept, where vasoconstriction in response to water loss across skin barriers can elevate systemic blood pressure, indicating that RAAS and vascular tone regulation extend beyond classical renal mechanisms [33].

The Sympathetic Nervous System (SNS) is another critical regulator of blood pressure, modulating heart rate, cardiac output, and peripheral vascular resistance. Enhanced SNS activity increases cardiac output and induces vasoconstriction, contributing to hypertension. Beta-adrenergic blockers exploit this mechanism to reduce blood pressure. Importantly, sex differences exist in SNS activity and its impact on blood pressure, with men exhibiting higher sympathetic tone and stronger correlations between catecholamine levels and ambulatory blood pressure than women, suggesting sex-specific therapeutic considerations [34]. The hypothalamic Paraventricular Nucleus (PVN) acts as a central autonomic control center, integrating excitatory and inhibitory neurotransmitters such as glutamate, GABA, nitric oxide, and angiotensin II to regulate sympathetic outflow and blood pressure. Dysregulation of PVN neurotransmission contributes to sympathetic overactivity and hypertension [35,36]. Moreover, the brain renin-angiotensin system, particularly angiotensin II type 1 receptors (AT1R) in circumventricular organs and PVN, modulates sympathetic tone and vasopressin release, linking central neurohormonal pathways to systemic blood pressure control [37-39]. Endo-

thelial function is pivotal in the regulation of vascular tone through the production of vasodilators, such as Nitric Oxide (NO). Endothelial dysfunction, characterized by reduced NO bioavailability, oxidative stress, and chronic inflammation, is closely associated with hypertension and atherosclerosis. This dysfunction impairs vasodilation, increases vascular resistance, and promotes vascular remodeling. Natural antioxidants and anti-inflammatory compounds, including polyphenols and flavonoids found in various herbal medicines, target these pathways to restore endothelial function and reduce blood pressure [40]. The role of endothelial ion channels and accessory proteins, such as phospholemman phosphorylation regulating vascular smooth muscle tone, further underscores the molecular complexity of endothelial contributions to blood pressure regulation [41].

The three core regulatory systems (RAAS, SNS, and endothelial function) intricately interact to maintain blood pressure homeostasis, and their cross-activation is a key feature of hypertension pathogenesis. RAAS overactivation not only directly induces vasoconstriction and sodium retention but also upregulates SNS activity via central and peripheral pathways, whereas enhanced sympathetic tone further stimulates renin release, forming a positive feedback loop [42]. Both RAAS activation and SNS overproduction induce excessive ROS generation, which impairs endothelial NO synthesis and bioavailability, and leads to endothelial dysfunction. Conversely, endothelial dysfunction reduces the inhibitory effect of NO on the RAAS and SNS, exacerbating their overactivation [43]. This interwoven regulatory network forms the multi-pathological basis of hypertension and provides a theoretical foundation for multi-target interventions using natural products. Collectively, these physiological systems, RAAS, sympathetic nervous system, and endothelial function, interact intricately to maintain blood pressure homeostasis. Their dysregulation underlies the pathogenesis of hypertension and provides multiple targets for pharmacological and natural therapeutic interventions.

Major Mechanistic Categories of Modern Chemical Antihypertensive Drugs

Modern pharmacological treatment of hypertension employs agents that target distinct physiological mechanisms to effectively lower blood pressure. Diuretics constitute a primary class that acts by promoting renal sodium and water excretion to reduce blood volume and cardiac output. Thiazide diuretics, such as hydrochlorothiazide, inhibit the Na-Cl cotransporter (NCC) in the distal convoluted tubule, a critical regulator of sodium reabsorption. Genetic and structural studies of NCC have elucidated its role in blood pressure control and modulation by thiazides, highlighting its importance as a therapeutic target [44]. Diuretics effectively decrease the preload and circulating volume, contributing to blood pressure reduction.

Vasodilators represent another major class, including Calcium Channel Blockers (CCBs) and agents targeting the RAAS. CCBs directly relax vascular smooth muscle by inhibiting calcium influx, thereby re-

ducing peripheral vascular resistance. RAAS inhibitors, such as ACEIs and ARBs, block the formation or action of angiotensin II, leading to vasodilation and decreased aldosterone-mediated sodium retention. These agents lower systemic vascular resistance and blood pressure. Novel insights into the molecular pathophysiology of angiotensin II receptors have refined understanding of their tissue-specific roles, informing therapeutic strategies [45]. Mineralocorticoid receptor antagonists, such as esaxerenone, provide additional vasodilatory and organ-protective effects without reflex sympathetic activation, underscoring the nuanced pharmacodynamics within this category [46].

Neural modulators, including central-acting antihypertensives and beta-adrenergic blockers, reduce sympathetic nervous system overactivity, which is a key contributor to hypertension. Beta-blockers decrease heart rate and cardiac output by antagonizing beta-adrenergic receptors, whereas central agents modulate sympathetic outflow from the brainstem. Emerging therapies, such as Transcranial Direct Current Stimulation (tDCS), have demonstrated potential in modulating autonomic balance and lowering ambulatory blood pressure in patients with hypertension, reflecting advances in neuromodulatory approaches [47]. Additionally, renal denervation, a catheter-based procedure targeting renal sympathetic nerves, has shown efficacy in reducing blood pressure by attenuating sympathetic drive, particularly in resistant hypertension [48-50]. These interventions highlight the therapeutic importance of neural regulation in blood pressure control. Overall, the pharmacological management of hypertension utilizes diuretics to reduce volume, vasodilators to decrease vascular resistance, and neural modulators to suppress sympathetic overactivity. Understanding the molecular and physiological bases of these drug classes facilitates personalized treatment strategies and integration with emerging therapies, including those derived from natural compounds that target overlapping pathways.

History and Application of Traditional Herbal Medicine in Hypertension Treatment

Wisdom of Hypertension Treatment in the Ayurvedic Medical System

Ayurveda, an ancient Indian medical system, conceptualizes hypertension not merely as an isolated pathological entity but as a manifestation of an imbalance among the fundamental bodily energies or doshas, primarily Vata and Pitta. This holistic framework emphasizes the maintenance of bodily equilibrium, viewing elevated blood pressure as a consequence of dysregulation in these doshas, which govern physiological and metabolic functions. Ayurvedic treatment strategies are inherently integrative, combining dietary modifications, lifestyle interventions, and herbal formulations to restore doshic balance and thereby control hypertension. For instance, classical Ayurvedic therapies such as Basti (medicated enemas) and Shirodhara (therapeutic oil pouring on the forehead) have demonstrated potential in reducing blood pressure and alleviating associated symptoms like palpitation,

insomnia, and fatigue, as evidenced by systematic reviews and meta-analyses of randomized controlled trials [51] Moreover, Ayurvedic herbal formulations like Raktadabashamak Ghana Vati and Sarpagandha Vati (containing Rauwolfia serpentina) have been clinically observed to lower systolic and diastolic blood pressure, sometimes enabling reduction or discontinuation of conventional antihypertensive medications [52] The integration of Ayurveda with lifestyle practices such as Yoga further enhances therapeutic outcomes by mitigating stress, a known contributor to hypertension [53] Traditional herbs like Butea monosperma (commonly known as purple flame tree) exemplify the Ayurvedic principle of utilizing the whole plant, with its seed powder recognized for diverse medicinal properties including antihypertensive effects, reflecting the system's ecological and pharmacological wisdom [54] Other botanicals frequently employed include Rauwolfia serpentina, whose active alkaloid reserpine is a well-established antihypertensive agent, as well as garlic and turmeric, which modern pharmacology confirms contain bioactive compounds with blood pressure-lowering and anti-inflammatory properties [55] Collectively, these approaches underscore Ayurveda's comprehensive and personalized methodology in managing hypertension, blending traditional knowledge with emerging scientific validation to offer a multifaceted therapeutic paradigm.

Forms and Advantages of Traditional Herbal Applications

Traditional Ayurvedic herbal medicines are administered in diverse forms, such as decoctions (kashayas), powders, pills (vatis), and tinctures (aristas or asavas), each tailored to optimize bioavailability and therapeutic efficacy. Central to Ayurvedic pharmacology is the concept of polyherbal formulations, in which multiple herbs are combined synergistically to enhance efficacy and mitigate potential toxicity, reflecting a sophisticated understanding of phytochemical interactions. This multicomponent approach aims to target various pathophysiological pathways simultaneously, thereby improving clinical outcomes in complex conditions, such as hypertension [27]. Compared to conventional chemical drugs, many herbal therapies are perceived to offer superior safety profiles with fewer adverse effects, attributable to their natural origin and balanced formulations. Additionally, traditional herbal medicines often exhibit greater accessibility and cost-effectiveness, particularly in low- and middle-income regions where healthcare resources are limited, thus sustaining their widespread use and cultural acceptance [52] However, despite these advantages, traditional herbal applications face significant challenges in standardization and quality control. Variability in plant species, harvesting conditions, and preparation methods leads to inconsistent dosages and uncertain concentrations of active constituents, complicating reproducibility and clinical validation [27] Moreover, the lack of rigorous identification and quantification of bioactive compounds impedes integration with modern pharmacotherapy and regulatory approval. Efforts to address these gaps include the development of standardized extracts, advanced analytical characterization of for-

mulations, such as Hridayarnava Rasa, an herbal-mineral Ayurvedic compound, and clinical trials employing double-blind, placebo-controlled designs to evaluate efficacy and safety [15,56]. Thus, while traditional herbal medicines offer promising complementary options for hypertension management, bridging the divide between traditional wisdom and modern scientific rigor remains essential to fully harness their therapeutic potential.

Antihypertensive Active Ingredients and Pharmacological Mechanisms of Representative Natural Herbs

Chemical Composition and Multi-Target Actions of Butea Monosperma

Butea monosperma is a medicinal plant renowned for its rich phytochemical profile, which underpins its diverse pharmacological activities, including antihypertensive effects. The plant contains a variety of bioactive compounds, such as flavonoids, terpenoids, steroids, and tannins, each contributing to its therapeutic potential. Among these, flavonoids, such as butein and butyrin, are particularly notable for their biological activities. For instance, butein-enriched fractions from B. monosperma flowers have demonstrated significant metabolic effects, including the induction of thermogenic genes such as Uncoupling Protein 1 (Ucp1), which enhances energy expenditure and may indirectly influence cardiovascular health by modulating metabolic parameters linked to hypertension [57] The flavonoid content, confirmed through HPLC and other phytochemical analyses, includes compounds such as apigenin derivatives and genistin, which have been implicated in antioxidant and enzyme inhibitory activities relevant to vascular function [58,59]. The antihypertensive mechanisms of B. monosperma are likely multifactorial and involve several pathways. The flavonoids present in the plant exhibit vasodilatory effects, potentially mediated by enhancing endothelial Nitric Oxide (NO) production or blocking calcium channels, leading to relaxation of vascular smooth muscle and subsequent reduction in blood pressure. The antioxidant properties of these compounds mitigate oxidative stress within the vasculature, thereby improving endothelial function and reducing vascular inflammation, which are critical factors in the pathogenesis of hypertension [60]. Additionally, some constituents may exert mild diuretic effects and modulate the Renin-Angiotensin-Aldosterone System (RAAS), further contributing to blood pressure control, although direct evidence for these effects in B. monosperma remains to be fully elucidated.

In addition to its antihypertensive potential, B. monosperma has a long history of traditional use in treating gastrointestinal disorders, such as diarrhea and constipation, as well as infections and liver ailments. These uses suggest the presence of anti-inflammatory, antimicrobial, and organ-protective bioactivities. For example, seed lectins isolated from B. monosperma have demonstrated antimicrobial efficacy against polymicrobial biofilms, including uropathogenic

Escherichia coli and *Candida albicans*, by disrupting microbial virulence factors and biofilm formation [61,62]. Such antimicrobial and anti-inflammatory properties may indirectly support long-term blood pressure regulation by reducing systemic inflammation and preventing infection-related vascular damage. Furthermore, the plant's extracts have shown promise in wound healing and tissue regeneration, indicating organ-protective effects that could be beneficial in hypertensive patients prone to vascular injury [63].

The chemical constituents of *B. monosperma* include lectins, which have been studied for their carbohydrate-binding specificity and potential biomedical applications. Butea Monosperma Agglutinin (BMA), a lectin purified from seeds, binds specifically to galactose and N-acetylgalactosamine residues and has been investigated as a biomarker in cholangiocarcinoma, highlighting the plant's diverse bioactive molecule repertoire [64,65]. These lectins, when conjugated with antimicrobial lipids, enhance antibacterial activity and reduce microbial resistance, further underscoring the multifunctional nature of *B. monosperma* phytochemicals [66]. In summary, the chemical composition of *B. monosperma* is characterized by a complex mixture of flavonoids, terpenoids, steroids, tannins, and lectins, which collectively contribute to its multi-target pharmacological actions. These include vasodilation via NO modulation and calcium channel blockade, antioxidant and anti-inflammatory effects improving endothelial function, mild diuretic and RAAS regulatory activities, and antimicrobial and organ-protective properties. This multifaceted pharmacology aligns with its traditional uses and supports its potential as a natural antihypertensive agent with broad systemic benefits.

Other Key Plant-Derived Bioactive Molecules and Their Mechanisms

In addition to *Butea monosperma*, several other botanicals have been extensively studied for their bioactive constituents and mechanisms relevant to hypertension management. Garlic (*Allium sativum*) is a prime example, with its organic sulfur compounds, such as allicin and diallyl disulfide, playing pivotal roles in cardiovascular protection. These compounds stimulate the endogenous production of gaseous signaling molecules, such as Hydrogen Sulfide (H₂S) and Nitric Oxide (NO), which are potent vasodilators that relax vascular smooth muscle and lower blood pressure. Garlic's bioactives also exhibit antioxidant properties by scavenging reactive oxygen species (ROS) and thereby preserving endothelial function. Moreover, garlic components have been shown to exert mild inhibition of Angiotensin-Converting Enzyme (ACE), contributing to the attenuation of the renin-angiotensin system and further supporting antihypertensive effects [58]. Olive leaf (*Olea europaea*) extracts contain oleuropein as a major active constituent, which demonstrates robust antioxidant and anti-inflammatory activities. Oleuropein improves endothelial function by enhancing NO bioavailability and reducing oxidative stress. It also modulates calcium channels, leading to vasodilation, and influences renin activity, thereby exerting a regulatory effect on the RAAS

pathway. These combined actions contribute to the lowering of systemic blood pressure and protection against vascular damage [58].

Flavonoids and polyphenols, widely distributed in tea, grapes, cocoa, and other plant sources, represent a broad class of bioactive molecules with significant cardiovascular benefits. Their mechanisms include enhancement of NO signaling pathways, which promotes vasodilation and reduces vascular resistance. They also inhibit ACE activity, decreasing angiotensin II production and its vasoconstrictive effects. Additionally, flavonoids and polyphenols reduce the generation of ROS and suppress the expression of pro-inflammatory cytokines, thereby mitigating endothelial dysfunction and vascular inflammation, key contributors to hypertension and cardiovascular disease progression [58].

The integration of these plant-derived bioactives into therapeutic strategies offers a multi-pronged approach to hypertension management. By targeting endothelial function, oxidative stress, inflammation, and neurohormonal regulation, these compounds provide complementary mechanisms that may enhance efficacy and reduce side effects compared to conventional monotherapies. Furthermore, their presence in commonly consumed foods and supplements facilitates their incorporation into lifestyle interventions aimed at reducing cardiovascular risk. In conclusion, bioactive molecules from garlic, olive leaf, and flavonoid/polyphenol-rich plants exert antihypertensive effects through synergistic mechanisms involving vasodilation via NO and H₂S pathways, antioxidant and anti-inflammatory actions, ACE inhibition, calcium channel modulation, and RAAS regulation. These multifaceted effects underscore the therapeutic potential of plant-derived compounds in cardiovascular health and highlight the importance of continued research to optimize their clinical applications.

The Emerging Role of Marine Resource Bioactive Components in Hypertension Treatment

Bioactive Antihypertensive Peptides Derived from Seafood Sources

Bioactive peptides derived from seafood, including fish, shellfish, and marine algae, have garnered significant attention owing to their potent antihypertensive properties, particularly through Angiotensin-Converting Enzyme (ACE) inhibition. These peptides, such as those containing valine-tyrosine-proline, are typically obtained via enzymatic hydrolysis of marine proteins, which releases short-chain peptides capable of modulating blood pressure by targeting the Renin-Angiotensin-Aldosterone System (RAAS). The mechanism of action of these peptides closely resembles that of synthetic ACE inhibitors, which block the conversion of angiotensin I to the vasoconstrictor angiotensin II, thereby promoting vasodilation and reducing blood pressure. However, marine-derived peptides may offer enhanced selectivity and fewer side effects compared to synthetic drugs, potentially due to their natural origin and specific amino acid sequences that confer targeted ACE inhibition [67]. In addition to ACE

inhibition, these peptides exhibit multifaceted cardiovascular benefits through complementary mechanisms. They enhance bradykinin activity, a vasodilatory peptide that further contributes to lowering vascular resistance. Additionally, their antioxidant properties mitigate oxidative stress, a key contributor to endothelial dysfunction and hypertension. Anti-inflammatory effects also play a crucial role, as chronic low-grade inflammation is implicated in the pathogenesis of hypertension. These combined actions synergistically improve vascular health and blood pressure regulation.

Importantly, marine peptides generally demonstrate favorable bioavailability and digestibility, which are critical for their efficacy as oral antihypertensive agents. Their low allergenic potential further supports their suitability for therapeutic use. Advances in extraction technologies, such as enzymatic hydrolysis assisted by ultrasound or microwaves, have improved yields and preserved the bioactivity of these peptides, facilitating their development as nutraceuticals or functional food ingredients [68]. Moreover, the valorization of seafood by-products, such as fish scales and bones, as sources of collagen and bioactive peptides aligns with sustainable practices, offering an eco-friendly approach to hypertension management. The integration of these peptides into delivery systems, such as nanoliposomes, enhances their stability and bioavailability, potentially increasing their clinical efficacy. Collectively, marine-derived antihypertensive peptides represent a promising natural alternative or adjunct to conventional pharmacotherapy, combining traditional wisdom with modern scientific validation to address hypertension through multiple molecular pathways [69].

Omega-3 Polyunsaturated Fatty Acids and Minerals from Seafood

Omega-3 Polyunsaturated Fatty Acids (PUFAs), particularly eicosapentaenoic acid (EPA) and Docosahexaenoic Acid (DHA), abundant in deep-sea fish oils, have been extensively studied for their cardiovascular benefits, including modest blood pressure-lowering effects. These fatty acids exert their antihypertensive action primarily through anti-inflammatory pathways mediated by their bioactive derivatives, such as resolvins, protectins, and maresins. These specialized pro-resolving mediators actively resolve vascular inflammation, a critical factor in endothelial dysfunction and hypertension pathogenesis. By improving endothelial function, omega-3 PUFAs enhance nitric oxide bioavailability, leading to vasodilation and reduced vascular resistance. Furthermore, they decrease the sensitivity of blood vessels to vasoconstrictive agents, thereby contributing to blood pressure regulation [67]. Although the direct hypotensive effect of omega-3 fatty acids is generally mild, their role in improving overall vascular health and reducing cardiovascular risk is well established. In addition to fatty acids, seafood is a rich source of essential minerals, such as potassium, magnesium, and calcium, which are vital for maintaining electrolyte balance and vascular smooth muscle tone. Potassium intake counteracts the hypertensive effects of high sodium

consumption by promoting natriuresis and vasodilation. Magnesium acts as a natural calcium antagonist, relaxing vascular smooth muscle, and preventing vasoconstriction. Calcium is crucial for vascular contractility and signaling, and adequate intake supports normal blood pressure regulation. Supplementation with these minerals from seafood sources has been shown to mitigate the blood pressure-raising effects of high-sodium diets, a common contributor to hypertension worldwide [70].

The synergistic presence of omega-3 PUFAs and minerals in seafood provides a multifactorial approach to blood pressure control, combining anti-inflammatory, vasodilatory, and electrolyte-regulating effects. This integrative nutritional profile supports the use of seafood-derived nutrients as complementary strategies in hypertension management. However, challenges remain in optimizing the bioavailability and stability of these compounds in functional foods or supplements. Technological innovations and rigorous clinical trials are needed to substantiate their efficacy and safety fully. Nonetheless, the incorporation of omega-3 fatty acids and minerals from marine sources into dietary interventions represents a scientifically grounded approach that bridges traditional dietary wisdom with contemporary cardiovascular research, offering a holistic means to combat hypertension and improve vascular health [67,70].

Comparison of Mechanisms of Action and Synergistic Potential Between Natural Products and Chemical Drugs

Comparative Analysis of Therapeutic Targets

Both natural herbal medicines and chemical drugs for hypertension prominently focus on the renin-Angiotensin-Aldosterone System (RAAS) and endothelial Nitric Oxide (NO) system as their core therapeutic targets. Chemical antihypertensive agents such as Angiotensin-Converting Enzyme Inhibitors (ACEIs) exert direct and potent inhibition on ACE, leading to rapid and significant reductions in angiotensin II levels and subsequent vasodilation. This targeted mechanism allows for precise dose control and predictable pharmacodynamics. In contrast, natural products, including certain peptides and polyphenols derived from plants, tend to modulate these systems more subtly and often through multiple points of intervention. For example, polyphenolic compounds can enhance Endothelial NO Synthase (eNOS) activity, thereby increase NO bioavailability and improving endothelial function, while also exerting antioxidant effects that indirectly support RAAS balance by reducing oxidative stress-induced RAAS activation [71,72]. This multitargeted modulation by natural products reflects a “multicomponent, multitarget, multipathway” mode of action, which contrasts with the single-target specificity of chemical drugs. The unique advantages of chemical drugs lie in their well-defined pharmacokinetics and pharmacodynamics, enabling rapid onset of action and precise titration. For instance, ACEIs and angiotensin receptor blockers (ARBs) have clearly delineated molec-

ular targets and dose-response relationships, facilitating their use in the management of acute and chronic hypertension. However, their single-target focus may limit their capacity to address the complex pathophysiology of hypertension, which often involves oxidative stress, inflammation, and organ remodeling.

Conversely, natural products often provide comprehensive benefits beyond blood pressure reduction. Their antioxidant, anti-inflammatory, and organ-protective properties contribute to mitigating hypertension-related complications such as vascular remodeling, renal injury, and metabolic disturbances [71,73]. For example, compounds like sinapine have been shown to inhibit the α_q -PLC β 3 axis, attenuating RAAS overactivation and providing cardiovascular protection with potentially fewer side effects than selective chemical inhibitors [74]. Moreover, natural products may influence mitochondrial and endoplasmic reticulum interactions, crucial in cardiovascular health, thereby offering novel therapeutic avenues [75]. This integrative approach of natural products may be particularly advantageous for long-term hypertension management and prevention of comorbidities, as it addresses multiple pathological processes simultaneously. However, the complexity of natural product pharmacology also poses challenges in standardization, dose optimization, and mechanistic elucidation. In summary, while chemical drugs provide rapid, potent, and specific inhibition of key hypertensive pathways, such as the RAAS and endothelial NO, natural products offer a broader, multi-targeted modulation that encompasses antioxidative and anti-inflammatory effects, potentially enhancing long-term cardiovascular protection and reducing hypertensive complications.

Synergistic Effects and Rationality of Combined Use

The theoretical basis for combining natural herbal medicines with conventional antihypertensive drugs lies in their complementary mechanisms and potential synergistic effects. For instance, certain herbal extracts possess mild diuretic and antioxidant properties that can enhance the efficacy of standard diuretics while mitigating their adverse effects, such as electrolyte imbalance and oxidative stress. This synergy may result in improved blood pressure control with reduced side effects. For example, polyphenols and omega-3 fatty acids found in natural products have demonstrated antiplatelet and antioxidant activities that can complement the vasodilatory and volume-reducing effects of chemical antihypertensives [76]. Such combinations may also address the multifactorial nature of hypertension by targeting oxidative stress, inflammation, and endothelial dysfunction concurrently. Clinical evidence supports the adjunctive use of natural products with conventional drugs. Trials incorporating garlic extract, hawthorn extract, or fish oil alongside standard antihypertensive regimens have reported modest additional reductions in blood pressure and improvements in lipid profiles and vascular function markers [71]. These findings suggest that natural products can enhance cardiovascular risk factor management beyond blood pressure lowering alone. However, the magnitude of blood pressure reduction is gener-

ally modest, indicating that natural products serve best as complementary rather than primary therapies.

Despite these benefits, caution is warranted due to potential herb-drug interactions. Some herbal compounds may alter the pharmacokinetics or pharmacodynamics of conventional drugs, leading to enhanced or diminished drug effects. For example, certain herbs can potentiate or inhibit the activity of warfarin or specific antihypertensive agents, increasing the risk of bleeding or loss of blood pressure control [77]. Therefore, the combined use of herbs and drugs should be guided by healthcare professionals with careful monitoring to avoid adverse interactions. Additionally, variability in herbal product quality and composition poses challenges for consistent therapeutic outcomes. In conclusion, the combined application of natural herbal medicines and chemical antihypertensive drugs is rational and potentially beneficial because of their complementary mechanisms and synergistic effects. Clinical studies have provided preliminary evidence of enhanced efficacy and improved cardiovascular parameters with such combinations. However, careful consideration of herb-drug interactions and individualized medical supervision are essential to ensure safety and optimize therapeutic outcomes in the management of hypertension.

Modern Research Methods Drive the Transformation and Verification of Traditional Wisdom

Isolation, Identification, and Structural Modification of Active Components

The isolation and identification of active antihypertensive components from traditional herbal medicines have been greatly advanced by modern analytical techniques, such as chromatography, Mass Spectrometry (MS), and Nuclear Magnetic Resonance (NMR) spectroscopy. These technologies enable the efficient separation and structural elucidation of bioactive compounds from complex plant matrices, thereby overcoming the challenges posed by the chemical diversity and complexity inherent in natural products. For example, the isolation of reserpine from *Rauwolfia serpentina* (Indian snakeroot) exemplifies how a specific alkaloid with potent blood pressure-lowering effects was identified, providing a lead compound for modern antihypertensive drug development. Contemporary metabolomics approaches, particularly MS-based metabolomics, have streamlined the discovery process by enabling rapid profiling and annotation of metabolites correlated with biological activity, thus guiding bioassay-directed fractionation and isolation. Platforms such as LC-MS and LC-MS/MS combined with bioinformatics tools (e.g., MetaboAnalyst, GNPS) facilitate the discrimination of active versus inactive fractions, expediting the identification of candidate molecules with antihypertensive potential. Additionally, Nuclear Magnetic Resonance Heterocovariance Analysis (NMR-HetCA) has emerged as a powerful chemometric method to directly link bioactivity with specific metabolites in complex mixtures prior to isolation, thereby enhancing the efficiency of natural product drug discovery.

Following isolation, structural modification of natural active components is a critical step to optimize their pharmacological properties. Chemical modifications aim to enhance potency, selectivity, and pharmacokinetic profiles, such as bioavailability and half-life, while reducing toxicity. Common strategies include functional group transformations, introduction of hydrophilic or lipophilic moieties, and conjugation with other pharmacophores. For instance, the Mannich reaction has been widely applied to natural products to introduce nitrogen-containing groups, thereby improving water solubility and biological activity. Similarly, cinnamic acid derivatives have been employed to enhance the anti-inflammatory, anticancer, and antihypertensive activities of parent natural compounds. Phosphorylation and glycosylation modifications have also been utilized to improve stability and bioactivity, as observed in flavonoids and terpenoids. Advances in synthetic biology and genome mining have facilitated the generation of novel analogs through heterologous expression and enzymatic tailoring, thereby expanding the chemical diversity accessible for drug development. These modifications are guided by Structure-Activity Relationship (SAR) studies and computational modeling to rationally design derivatives with improved efficacy and safety profiles. Overall, the integration of modern analytical techniques with medicinal chemistry approaches enables the transformation of traditional herbal constituents into optimized lead compounds for antihypertensive therapy.

In-Depth Studies on Molecular Mechanisms and Signaling Pathways

Understanding the molecular mechanisms and signaling pathways modulated by natural antihypertensive compounds is essential for elucidating their therapeutic actions and optimizing their clinical applications. Advanced cellular and molecular biology techniques, including the use of specific cell models, gene knockout/knockin animal models, and molecular probes, have been instrumental in dissecting the precise targets and pathways influenced by these natural products. For example, oleuropein from olive and marine-derived peptides have been shown to regulate ion channels, enzyme activities, and gene expression involved in vascular tone and blood pressure regulation. These studies reveal that natural products can modulate calcium channels, nitric oxide synthase activity, and inflammatory mediators, thereby exerting vasodilatory, anti-inflammatory, and antioxidant effects critical for antihypertensive efficacy. Systems biology and network pharmacology approaches have further advanced the understanding of the complex interactions among multiple components in herbal formulations and their collective impact on hypertension-related biological networks. By integrating multi-omics data and computational modeling, these methods elucidate how various phytochemicals synergistically regulate signaling cascades, such as the Renin-Angiotensin-Aldosterone System (RAAS), oxidative stress pathways, and endothelial function. This holistic perspective provides a scientific rationale for traditional herbal combinations and supports

the identification of key bioactive constituents and their molecular targets. Moreover, network pharmacology facilitates the prediction of potential off-target effects and drug interactions, thereby enhancing the safety profile of natural antihypertensive therapies.

Recent research has highlighted the role of natural compounds in modulating epigenetic regulators and miRNAs involved in vascular remodeling and pathogenesis of hypertension. For instance, flavonoids and alkaloids have been reported to influence gene expression patterns through histone modification and DNA methylation, contributing to long-term vascular health benefits. Additionally, the gut microbiome has emerged as a novel mediator of the effects of natural products on blood pressure, with certain phytochemicals modulating microbial composition and metabolite production, thereby influencing systemic inflammation and neurogenic hypertension. In summary, the integration of molecular biology, systems pharmacology, and computational tools has provided profound insights into the multifaceted mechanisms by which natural products exert antihypertensive effects. These advances not only validate traditional medicinal knowledge but also guide the rational design of novel therapeutics that target complex Hypertension Pathophysiology.

Clinical Challenges, Safety Considerations, and Future Prospects

Standardization, Quality Control, and Evidence-Based Medicine

The therapeutic efficacy and safety of natural herbal products for hypertension are profoundly influenced by the variability in their active constituent content, which is affected by multiple factors, including geographic origin, harvesting season, and processing methods. This inherent heterogeneity poses significant challenges to ensuring consistent clinical outcomes and patient safety. Therefore, establishing rigorous standardization protocols encompassing cultivation, extraction, and quality control is indispensable. Standardized cultivation practices must consider soil composition, climate, and agronomic techniques to minimize variability in phytochemical profiles. Similarly, extraction methods require optimization to preserve bioactive compounds while eliminating contaminants. Quality control standards should incorporate advanced analytical techniques, such as High-Performance Liquid Chromatography (HPLC) and mass spectrometry, to quantify active ingredients and detect adulterants or toxins. These measures collectively form the foundation for reproducible therapeutic effects and safety assurance in herbal antihypertensive interventions. Despite the long-standing traditional use of many herbal remedies, the current evidence base is often limited by methodological shortcomings, small sample sizes, and short follow-up durations. To bridge this gap, there is an urgent need for well-designed, large-scale Randomized Controlled Trials (RCTs) with extended follow-up periods that rigorously evaluate the antihypertensive efficacy and safety profiles of specific herbs or their isolated compounds. Such

trials should adhere to CONSORT guidelines and incorporate clinically meaningful endpoints, including blood pressure reduction, target organ protection, and adverse event monitoring. High-quality evidence generated from these studies will provide the robust, evidence-based medicine foundation necessary to integrate herbal therapies into mainstream hypertension management, thereby complementing or potentially substituting conventional pharmacotherapy where appropriate. This approach not only addresses the limitations of empirical traditional medicine but also facilitates regulatory approval and clinical acceptance of herbal antihypertensive agents [78-80].

Safety, Interactions, and Personalized Treatment

Although natural products are often perceived as inherently safe, this assumption is misleading and potentially hazardous. Herbal medicines can exert hepatotoxic or nephrotoxic effects, and their complex phytochemical composition may adversely interact with conventional antihypertensive drugs, particularly through modulation of Cytochrome P450 (CYP450) enzyme systems. Such interactions can alter drug metabolism, leading to subtherapeutic effects or toxicity. For instance, certain herbal constituents may inhibit or induce CYP450 isoforms, affecting plasma concentrations of co-administered drugs, such as calcium channel blockers or angiotensin receptor blockers. Therefore, comprehensive pharmacovigilance and mechanistic studies are essential to elucidate these interactions and mitigate risks. In the future, the paradigm of “precision nutrition” or “personalized phytotherapy” represents a promising frontier.

By leveraging advances in genomics, metabolomics, and other omics technologies, it is possible to identify patient subpopulations with genetic or metabolic profiles predictive of enhanced responsiveness or susceptibility to adverse effects from specific herbal agents. For example, polymorphisms in genes encoding drug-metabolizing enzymes or transporters could inform individualized herbal treatment regimens, optimizing efficacy while minimizing toxicity. Integrating such personalized approaches into clinical practice requires multidisciplinary collaboration and the development of predictive biomarkers. Ultimately, this strategy aligns with the broader movement toward precision medicine, enabling tailored hypertension management that incorporates both synthetic drugs and natural products based on individual patient characteristics [78,79].

Integrative Medicine Models and Sustainable Development

The management of hypertension can significantly benefit from integrative medicine models that harmonize traditional wisdom with contemporary scientific validation. Such models advocate for the incorporation of evidence-based natural therapies as components of lifestyle interventions or as adjuncts to conventional pharmacotherapy, thereby creating a multi-tiered, individualized treatment framework. This holistic approach not only addresses the multifactorial etiology of hypertension but also enhances patient adherence and

satisfaction by offering diverse therapeutic options. Moreover, the development and utilization of multifunctional plants, such as *Butea monosperma*, exemplify the convergence of medical, environmental, and economic benefits. *Butea monosperma* possesses pharmacological properties relevant to cardiovascular health while simultaneously contributing to ecological sustainability and agricultural livelihoods. Promoting the cultivation and use of such plants aligns with global sustainable development goals by fostering biodiversity conservation, reducing reliance on synthetic chemicals, and supporting rural economies. Integrative hypertension management models that embed validated herbal therapies within broader public health strategies can thus advance both individual and planetary health. This synergy underscores the imperative for interdisciplinary research and policy frameworks that support sustainable, culturally sensitive, and scientifically grounded integrative medicine practices [78,80].

Conclusion

The evolution of hypertension treatment reflects a significant paradigm shift from reliance on single-agent chemical drugs toward a more integrative and multifaceted approach that harmonizes traditional herbal wisdom with contemporary pharmacological insights. This review elucidates that natural products, including terrestrial herbs (*Butea monosperma*, *Allium sativum*, *Olea europaea*) and emerging marine bioactive components (antihypertensive peptides, omega-3 PUFAs), exert antihypertensive effects via multi-targeted modulation of core pathways (RAAS, endothelial NO system, and sympathetic nervous system), with inherent advantages in terms of antioxidant, anti-inflammatory, and organ-protective activities. The combination of natural and synthetic drugs exhibits notable synergistic potential, capable of enhancing blood pressure control and reducing adverse effects. However, despite its promising therapeutic potential, the integration of NT into mainstream hypertension management is not without challenges. Inconsistent quality due to inadequate standardization of herbal preparations, insufficient high-quality large-scale RCT evidence for efficacy and safety, and potential herb-drug interactions. Therefore, future research should prioritize well-designed RCTs and systematic investigations into pharmacokinetics and pharmacodynamics to establish robust evidence bases.

Ultimately, the development of personalized integrative hypertension management represents the core research direction and integrative model that combines scientifically validated natural therapies with standardized pharmacological treatments and lifestyle modifications. Such a comprehensive approach capitalizes on the strengths of both traditional and modern medicine and aligns with the holistic principles of patient-centered care. In conclusion, the seamless integration of traditional herbal medicine and modern pharmacology is not only a scientific exploration of reconciling ancient wisdom with contemporary research, but also a practical approach to enrich the antihypertensive therapeutic arsenal. This paradigm shift will facilitate the development of more effective, safe, and personalized treatment

strategies, address the complex pathophysiology of hypertension and advance global cardiovascular disease prevention and control goals.

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